CLAIMS

What is claimed is:

1. A method of determining how the solubility of a solid compound-of-interest is affected by its form during a period between the early-lead optimization and clinical trials, which comprises:

(a) preparing an array of samples, each comprising a controlled amount of the compound-of-interest, wherein the form of the compound-of-interest in at least two of the samples is different;

(b) forming a liquid portion of each sample by adding a solvent to each sample; and

(c) determining how much compound-of-interest dissolved in the liquid portion of each sample.

2. The method of claim 1, wherein:

(a) the method further comprises separating the liquid portion of each sample from any solid portion each sample may contain prior to the determination;

(b) the solid remaining in a sample after separation of its liquid portion is analyzed to determine whether any change of form occurred;

(c) the physical form of the compound-of-interest in one sample differs from the physical form of the compound-of-interest in another sample;

(d) the compound-of-interest in one sample is amorphous and the compound-of-interest in another sample is crystalline;

(e) the compound-of-interest in one sample is crystalline and has a first crystal structure and/or a first crystal habit and the compound-of-interest in another sample is crystalline and has a second crystal structure and/or a second crystal habit, wherein the second crystal structure differs from the first crystal structure and/or the second crystal habit differs from the first crystal habit;

(f) the chemical form of the compound-of-interest in one sample differs from the chemical form of the compound-of-interest in another sample;

(g) the compound-of-interest in one sample is a salt, solvate, or co-crystal of a compound and the compound-of-interest in another sample is a different salt, solvate, or co-crystal of the compound;

(h) the compound-of-interest in one sample is a compound and the compound-of-interest in another sample is a salt, solvate, or co-crystal of the compound;

(i) the amount of compound-of-interest is less than about 100 micrograms;

(j) the amount of compound-of-interest is less than about 50 micrograms; or

(k) the amount of compound-of-interest is less than about 10 micrograms.

3. A method of determining how the dissolution of a solid compound-of-interest is affected by its form, which comprises:

(a) preparing an array of samples, each comprising a controlled amount of the compound-of-interest, wherein the form of the compound-of-interest in at least two of the samples is different;

(b) forming a liquid portion of each sample by adding a solvent to each sample; and

(c) determining how much compound-of-interest dissolved in the liquid portion of each sample as a function of time.

4. The method of claim 3, wherein:

(a) the method further comprises separating the liquid portion of each sample from any solid portion each sample may contain prior to the determination;

(b) the solid remaining in a sample after separation of its liquid portion is analyzed to determine whether any change of form occurred; or

(c) the method further comprises:

(i) preparing a first sub-array of samples, each comprising a controlled amount of the compound-of-interest in a first form;

(ii) preparing a second sub-array of samples, each comprising a controlled amount of the compound-of-interest in a second form that differs from the first form;

(iii) forming a liquid portion of each sample in the first sub-array by adding a controlled amount of a solvent to each sample in the first

sub-array at a time point that is unique to each sample in the first sub-array;

(iv) forming a liquid portion of each sample in the second sub-array by adding a controlled amount of a solvent to each sample in the second sub-array at a time point that is unique to each sample in the second sub-array but is the same as the time point at which solvent was added to a sample in the first sub-array;

(v) separating the liquid portion of each sample in the first and second sub-arrays from any solid portion each sample may contain at a time point that is the same for each sample in the first and second sub-arrays; and

(vi) determining how much compound-of-interest dissolved in the liquid portion of each sample;

(d) the physical form of the compound-of-interest in one sample differs from the physical form of the compound-of-interest in another sample;

(e) the compound-of-interest in one sample is amorphous and the compound-of-interest in another sample is crystalline;

(f) the compound-of-interest in one sample is crystalline and has a first crystal structure and/or a first crystal habit and the compound-of-interest in another sample is crystalline and has a second crystal structure and/or a second crystal habit, wherein the second crystal structure differs from the first crystal structure and/or the second crystal habit differs from the first crystal habit;

(g) the chemical form of the compound-of-interest in one sample differs from the chemical form of the compound-of-interest in another sample;

(h) the compound-of-interest in one sample is a salt, solvate, or co-crystal of a compound and the compound-of-interest in another sample is a different salt, solvate, or co-crystal of the compound;

(i) the compound-of-interest in one sample is a compound and the compound-of-interest in another sample is a salt, solvate, or co-crystal of the compound;

(j) the amount of compound-of-interest is less than about 100 micrograms;

(k) the amount of compound-of-interest is less than about 50 micrograms; or

(l) the amount of compound-of-interest is less than about 10 micrograms.

4. A method of determining how the stability of a solid compound-of-interest is affected by its form, which comprises:

(a) preparing an array of samples, each comprising a controlled amount of the compound-of-interest, wherein the form of the compound-of-interest in at least two of the samples is different;

(b) exposing the compound-of-interest in each sample to a condition that may affect the stability of the compound-of-interest; and

(c) determining whether the form or chemical composition of the compound-of-interest in each sample changed.

5. The method of claim 4 wherein:

(a) the condition is pH, ionic strength, counter-ion concentration, relative humidity, radiation, oxidative conditions, mechanical stress, temperature, or time;

(b) the physical form of the compound-of-interest in one sample differs from the physical form of the compound-of-interest in another sample;

(c) the compound-of-interest in one sample is amorphous and the compound-of-interest in another sample is crystalline;

(d) the compound-of-interest in one sample is crystalline and has a first crystal structure and/or a first crystal habit and the compound-of-interest in another sample is crystalline and has a second crystal structure and/or a second crystal habit, wherein the second crystal structure differs from the first crystal structure and/or the second crystal habit differs from the first crystal habit;

(e) the chemical form of the compound-of-interest in one sample differs from the chemical form of the compound-of-interest in another sample;

(f) the compound-of-interest in one sample is a salt, solvate, or co-crystal of a compound and the compound-of-interest in another sample is a different salt, solvate, or co-crystal of the compound;

(g) the compound-of-interest in one sample is a compound and the compound-of-interest in another sample is a salt, solvate, or co-crystal of the compound;

(h) the amount of compound-of-interest is less than about 100 micrograms;

(i) the amount of compound-of-interest is less than about 50 micrograms; or

(j) the amount of compound-of-interest is less than about 10 micrograms.

6. A method of determining how the hygroscopicity of a solid compound-of-interest is affected by its form, which comprises:

(a) preparing an array of samples, each comprising a controlled amount of the compound-of-interest, wherein the form of the compound-of-interest in at least two of the samples is different;

(b) exposing the compound-of-interest in each sample to a controlled relative humidity for a period of time; and

(c) determining the change in water content of the compound-of-interest in each sample.

7. The method of claim 6 wherein:

(a) the physical form of the compound-of-interest in one sample differs from the physical form of the compound-of-interest in another sample;

(b) the compound-of-interest in one sample is amorphous and the compound-of-interest in another sample is crystalline;

(c) the compound-of-interest in one sample is crystalline and has a first crystal structure and/or a first crystal habit and the compound-of-interest in another sample is crystalline and has a second crystal structure and/or a second crystal habit, wherein the second crystal structure differs from the first crystal structure and/or the second crystal habit differs from the first crystal habit;

(d) the chemical form of the compound-of-interest in one sample differs from the chemical form of the compound-of-interest in another sample;

(e) the compound-of-interest in one sample is a salt, solvate, or co-crystal of a compound and the compound-of-interest in another sample is a different salt, solvate, or co-crystal of the compound;

(f) the compound-of-interest in one sample is a compound and the compound-of-interest in another sample is a salt, solvate, or co-crystal of the compound;

(g) the amount of compound-of-interest is less than about 100 micrograms;

(h) the amount of compound-of-interest is less than about 50 micrograms; or

the amount of compound-of-interest is less than about 10 micrograms.

8. A method of determining the effect of a condition on the solubility of a compound-of-interest, which comprises:

(a) preparing an array of samples having a liquid portion, each comprising a controlled amount of the compound-of-interest and a solvent;

(b) exposing each sample to a condition that differs for at least two samples in the array; and

(c) determining how much compound-of-interest dissolved in the liquid portion of each sample.

9. The method of claim 8, wherein:

(a) the method further comprises separating the liquid portion of each sample from any solid portion each sample may contain prior to the determination;

(b) the solid remaining in a sample after separation of its liquid portion is analyzed to determine whether any change of form occurred;

(c) the condition is pH, ionic strength, counter-ion concentration, relative humidity, radiation, oxidative conditions, mechanical stress, temperature, or time;

(d) the amount of compound-of-interest is less than about 100 micrograms;

(e) the amount of of compound-of-interest is less than about 50 micrograms; or

(f) the amount of compound-of-interest is less than 10 micrograms.

10. A method of determining the effect of a condition on the dissolution of a compound-of-interest, which comprises:

(a) preparing an array of samples having a liquid portion, each comprising a controlled amount of the compound-of-interest and a solvent;

(b) exposing each sample to a condition that differs for at least two samples in the array; and

(c) determining how much compound-of-interest dissolved in the liquid portion of each sample as a function of time.

11. The method of claim 10, wherein:

(a) the method further comprises separating the liquid portion of each sample from any solid portion each sample may contain prior to the determination;

(b) the solid remaining in a sample after separation of its liquid portion is analyzed to determine whether any change of form occurred;

(c) the condition is pH, ionic strength, counter-ion concentration, relative humidity, radiation, oxidative conditions, mechanical stress, or temperature;

(d) the method further comprises:

(i) preparing a first sub-array of samples, each comprising a controlled amount of the compound-of-interest;

(ii) preparing a second sub-array of samples, each comprising a controlled amount of the compound-of-interest;
(iii) forming a liquid portion of each sample in the first sub-array by adding a solvent to each sample in the first sub-array at a time point that is unique to each sample in the first sub-array;
(iv) exposing each sample in the first sub-array to a first condition;
(v) forming a liquid portion of each sample in the second sub-array by adding a solvent to each sample in the second sub-array at a time point that is unique to each sample in the second sub-array but is the same as the time point at which solvent was added to a sample in the first sub-array;
(vi) exposing each sample in the second sub-array to a second condition that differs from the first condition;
(vii) separating the liquid portion of each sample in the first and second sub-arrays from any solid portion each sample may contain at a time point that is the same for each sample in the first and second sub-arrays; and
(viii) determining how much compound-of-interest dissolved in the liquid portion of each sample;

(e) the amount of compound-of-interest is less than about 100 micrograms;

(f) the amount of of compound-of-interest is less than about 50 micrograms; or

(g) the amount of compound-of-interest is less than 10 micrograms.

12. A method of determining the effect of a condition on the stability of a compound-of-interest, which comprises:

(a) preparing an array of samples, each comprising a controlled amount of the compound-of-interest, wherein the controlled amount is less than about 100 μg;

(b) exposing each sample to a condition that differs for at least two samples in the array; and

(c) determining whether the form or chemical composition of the compound-of-interest in each sample changed.

13. The method of claim 12, wherein:

(a) the condition is pH, ionic strength, counter-ion concentration, relative humidity, radiation, oxidative conditions, mechanical stress, temperature, or time;

(b) the amount of compound-of-interest is less than about 100 micrograms;

(c) the amount of of compound-of-interest is less than about 50 micrograms; or

(d) the amount of compound-of-interest is less than 10 micrograms.

14. A method of determining the effect of a condition on the hygroscopicity of a compound-of-interest, which comprises:

(a) preparing an array of samples, each comprising a controlled amount of the compound-of-interest;

(b) exposing the compound-of-interest in each sample to a controlled relative humidity for a period of time and to an additional condition that differs for at least two samples in the array; and

(c) determining the change in water content of the compound-of-interest in each sample.

15. The method of claim 14, wherein:

(e) the condition is pH, ionic strength, counter-ion concentration, radiation, oxidative conditions, mechanical stress, or temperature;

(f) the amount of compound-of-interest is less than about 100 micrograms;

(g) the amount of of compound-of-interest is less than about 50 micrograms; or

(h) the amount of compound-of-interest is less than 10 micrograms.

16. A method of determining the effect of an excipient on the solubility of a compound-of-interest, which comprises:

(a) preparing an array of samples having a liquid portion, each comprising a controlled amount of the compound-of-interest, a solvent, and an excipient, wherein the excipient or the amount of excipient differs for at least two of the samples; and

(b) determining how much compound-of-interest dissolved in the liquid portion of each sample.

17. The method of claim 16, wherein:

(a) the method further comprises separating the liquid portion of each sample from any solid portion each sample may contain prior to the determination;

(b) the solid remaining in a sample after separation of its liquid portion is analyzed to determine whether any change of form occurred;

(c) the amount of excipient in at least one sample is zero;

(d) the excipient is a diluent, binder, lubricant, stabilizing or neutralizing agent, packaging reagent, or processing reagent;

(e) the amount of compound-of-interest is less than about 100 micrograms;

(f) the amount of compound-of-interest is less than 50 micrograms; or

(g) the amount of compound-of-interest is less than 10 micrograms.

18. A method of determining the effect of an excipient on the dissolution of a compound-of-interest, which comprises:

(a) preparing an array of samples having a liquid portion, each comprising a controlled amount of the compound-of-interest, a solvent, and an excipient, wherein the excipient or the amount of excipient differs for at least two of the samples; and

(b) determining how much compound-of-interest dissolved in the liquid portion of each sample as a function of time.

19. The method of claim 18, wherein

(a) the method further comprises separating the liquid portion of each sample from any solid portion each sample may contain prior to the determination;

(b) the solid remaining in a sample after separation of its liquid portion is analyzed to determine whether any change of form occurred; or

(c) the method further comprising:

(i) preparing a first sub-array of samples, each comprising a controlled amount of the compound-of-interest and a first excipient;

(ii) preparing a second sub-array of samples, each comprising a controlled amount of the compound-of-interest and a second excipient that differs from the first excipient and/or is provided in a different amount than the first excipient;

(iii) forming a liquid portion of each sample in the first sub-array by adding a solvent to each sample in the first sub-array at a time point that is unique to each sample in the first sub-array;

(iv) forming a liquid portion of each sample in the second sub-array by adding a solvent to each sample in the second sub-array at a time point that is unique to each sample in the second sub-array but is the same as the time point at which solvent was added to a sample in the first sub-array;

(v) separating the liquid portion of each sample in the first and second sub-arrays from any solid portion each sample may contain at a time point that is the same for each sample in the first and second sub-arrays; and

(vi) determining how much compound-of-interest dissolved in the liquid portion of each sample;

(d) the amount of excipient in at least one sample is zero;

(e) the excipient is a diluent, binder, lubricant, stabilizing or neutralizing agent, packaging reagent, or processing reagent;

(f) the amount of compound-of-interest is less than about 100 micrograms;

(g) the amount of compound-of-interest is less than 50 micrograms; or

(h) the amount of compound-of-interest is less than 10 micrograms.

20. A method of determining the effect of an excipient on the stability of a compound-of-interest, which comprises:

(a) preparing an array of samples, each of which comprises a controlled amount of the compound-of-interest and an excipient, wherein the excipient or the amount of excipient differs for at least two of the samples;

(b) exposing the samples to a condition that may affect the stability of the compound-of-interest; and

(c) determining whether the form or chemical composition of the compound-of-interest in each sample changed.

21. The method of claim 20, wherein:

(a) the condition is pH, ionic strength, counter-ion concentration, relative humidity, radiation, oxidative conditions, mechanical stress, temperature, or time;

(b) the amount of excipient in at least one sample is zero;

(c) the excipient is a diluent, binder, lubricant, stabilizing or neutralizing agent, packaging reagent, or processing reagent;

(d) the amount of compound-of-interest is less than about 100 micrograms;

(e) the amount of compound-of-interest is less than 50 micrograms; or

(f) the amount of compound-of-interest is less than 10 micrograms.

22. A method of determining the effect of an excipient on the hygroscopicity of a compound-of-interest, which comprises:

(a) preparing an array of samples, each of which comprises a controlled amount of the compound-of-interest and an excipient, wherein the excipient or the amount of excipient differs for at least two of the samples;

(b) exposing the samples to a controlled relative humidity for a period of time; and

(c) determining the change in water content of the compound-of-interest in each sample.

23. The method of claim 22, wherein:

(g) the amount of excipient in at least one sample is zero;

(h) the excipient is a diluent, binder, lubricant, stabilizing or neutralizing agent, packaging reagent, or processing reagent;

(i) the amount of compound-of-interest is less than about 100 micrograms;

(j) the amount of compound-of-interest is less than 50 micrograms; or

(k) the amount of compound-of-interest is less than 10 micrograms.